Applied Medical Informatics
Original Research Vol. 47, No.4/2025, pp 166-177

A Systems Biology Approach to miRNA–mRNA Regulatory Networks in Age-Related Macular Degeneration: Network Topology and Pathway Enrichment

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Received: 23 October 2025/Accepted: 19 December 2025/ Published online: 21 December 2025

Abstract
Purpose: The study aimed to explore the role of microRNA (miRNA)–messenger RNA (mRNA) interactions in age-related macular degeneration (AMD) using a systems biology framework. *Methods:* A comprehensive literature review was conducted to curate experimentally validated miRNA–mRNA interactions related to AMD. A bipartite interaction network was constructed and analyzed using network topology measures, including degree and betweenness centrality, to identify key regulators. Community detection was performed using the Louvain algorithm, and functional enrichment analysis of target genes was conducted using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases with multiple-testing correction. *Results:* The network comprised 125 nodes and 100 edges. *VEGFA, BCL2, SIRT1,* and *IL6* emerged as hub genes, while *VEGFA* and *STAT3* were key bottlenecks. Community detection revealed five modules enriched in functionally coherent genes. GO analysis highlighted inflammation, angiogenesis, oxidative stress, apoptosis, and extracellular matrix regulation. KEGG analysis identified VEGF, PI3K-Akt, NF-κB, TGF-β, and complement signaling pathways. *Conclusions:* The findings provide systems-level insight into coordinated post-transcriptional regulation in AMD and support the potential of miRNAs as biomarkers and multi-target therapeutic candidates.

Keywords*:* Age-related macular degeneration; microRNAs (miRNA); messenger RNAs (mRNA); Network Analysis; Functional Enrichment

Introduction

Age-related macular degeneration (AMD) is a complex, multifactorial retinal disorder and a leading cause of irreversible vision loss in the elderly. The disease results from progressive dysfunction and degeneration of the retinal pigment epithelium (RPE), Bruch's membrane, and choriocapillaris, leading ultimately to photoreceptor loss. AMD manifests clinically as two major forms: the non-exudative (atrophic) and exudative (neovascular) types. Both forms share a multifaceted pathophysiology involving inflammation, oxidative stress, apoptosis, mitochondrial dysfunction, and aberrant angiogenesis [1,2]. Despite advances in understanding its genetic and environmental risk factors, the precise molecular mechanisms underlying AMD remain incompletely understood. Emerging evidence suggests that dysregulation of post-transcriptional gene regulation by microRNAs (miRNAs) plays a critical role in AMD pathogenesis by modulating key biological processes such as inflammation, angiogenesis, oxidative stress, and apoptosis [3,4].

MicroRNAs (miRNAs) have emerged as pivotal regulators of gene expression in health and disease, acting post-transcriptionally by repressing target messenger RNAs (mRNAs) [5]. In the retina, miRNAs maintain tissue

homeostasis and participate in processes such as photoreceptor maintenance, RPE differentiation, and response to oxidative damage [6,7]. Dysregulation of miRNAs has been reported in both experimental models and patients with AMD, implicating them as crucial modulators of disease onset and progression [8]. However, while many studies have identified individual miRNAs associated with AMD, their broader regulatory relationships and interaction networks remain underexplored.

Systems biology and network-based approaches provide powerful tools to analyze complex regulatory relationships on a genome-wide scale [9]. Constructing miRNA–mRNA interaction networks allows identification of hub regulators, key network modules, and potential functional pathways that drive disease processes [10]. Integrating functional enrichment analyses, such as Gene Ontology and KEGG pathway analysis, enables the identification of biological processes and signaling pathways significantly associated with disease-related miRNA targets.

To address this gap, the present study employed a **systems biology approach** to delineate the miRNA–mRNA regulatory landscape of AMD using literature-curated interactions. By integrating network topology analysis, community detection through the Louvain algorithm, and functional enrichment analysis, we aimed to identify central regulatory hubs, functional modules, and enriched pathways that may contribute to AMD pathophysiology.

In this study, we employed a systems biology approach to construct and analyze an AMD-specific miRNA–mRNA regulatory network. Comprehensive network topology analyses were performed to identify hub miRNAs and mRNAs, followed by functional enrichment of target genes to reveal key biological processes and pathways implicated in AMD. Our integrative analysis provides novel insights into the post-transcriptional regulatory landscape of AMD and may inform the development of miRNA-based diagnostic and therapeutic strategies.

Materials and Methods

Data Collection of miRNA–mRNA Interactions

A comprehensive literature review was conducted to identify microRNAs (miRNAs) associated with Age-Related Macular Degeneration (AMD) and their experimentally validated target genes. Relevant studies were screened from publicly available sources, including peer-reviewed articles, databases, and supplementary materials. In total, 100 miRNA–mRNA pairs were curated, representing interactions with strong experimental evidence or consistent validation in AMD-related studies [3,11-13].

Construction of the miRNA–mRNA Interaction Network

The curated miRNA–mRNA pairs were used to construct a bipartite interaction network using Python and the NetworkX library. In this network, miRNAs and mRNAs were represented as distinct sets of nodes, and interactions between them were represented as edges. Node attributes were assigned according to node type (miRNA or mRNA) for visualization and network analysis purposes. A force-directed layout algorithm was applied to optimize the spatial representation of the network.

Network Topology Analysis

Advanced network analysis was performed to investigate the structural properties and identify key regulatory components of the network. The following metrics were computed:

- **Degree centrality** to identify hub nodes with the highest number of interactions.
- **Betweenness centrality** to determine nodes that bridge different network modules.
- **Network density** to evaluate the overall connectivity of the network.
- **Community detection** using the Louvain community detection algorithm to identify densely connected modules within the network.

Functional Enrichment Analysis

Functional enrichment of the target genes was performed using the gseapy Python package, interfacing with Enrichr. Two types of analyses were conducted:

1. **Gene Ontology (GO) Biological Process enrichment**, to identify biological processes significantly associated with the target genes.
2. **KEGG pathway enrichment**, to determine signaling pathways enriched among the target genes.

For each analysis, adjusted p-values were calculated to account for multiple testing, and terms with adjusted p-values < 0.05 were considered significant. The top enriched GO terms and KEGG pathways were visualized using bar plots, highlighting the significance and proportion of genes involved in each term or pathway.

Software and Tools

All analyses were performed using Python (version 3.12), with the following key libraries: NetworkX for network construction and topology analysis, gseapy for enrichment analysis, and Matplotlib and Seaborn for visualization.

Results

Network Construction and General Characteristics

A total of 100 experimentally validated miRNA–mRNA interaction pairs associated with age-related macular degeneration (AMD) were retrieved through an extensive literature review. After removing duplicates, the network comprised 83 nodes (20 miRNAs and 63 mRNAs) and 100 edges, representing directed regulatory interactions between miRNAs and their respective target genes (Figure 1). The bipartite network displayed a sparse but structured topology, consistent with biological networks where few nodes act as regulatory hubs. The global network density was calculated to be 0.029, confirming a low degree of random connectivity but indicating selective and biologically meaningful relationships among the nodes.

Visual inspection of the network revealed that several miRNAs regulated multiple target genes, while specific mRNAs were commonly targeted by different miRNAs, indicating potential cross-regulatory mechanisms and redundant control pathways in AMD. This configuration suggests that a small subset of highly connected nodes may exert substantial influence over the overall system behavior.

A bipartite network constructed from 100 experimentally validated miRNA–mRNA pairs associated with AMD. Green nodes represent mRNAs, and red nodes represent miRNAs. Edge connections indicate regulatory interactions. The network demonstrates a sparse but organized topology, with several highly connected hub nodes exerting major regulatory influence.

Network Topology and Identification of Key Regulators

To identify the central regulators within the network, topological parameters such as **degree centrality** and **betweenness centrality** were computed. The top 10 nodes are presented in Table 1.

- Based on degree centrality, the most highly connected nodes were vascular endothelial growth factor A (*VEGFA)* (0.122), B-cell lymphoma 2 (*BCL2)* (0.085), Sirtuin 1 (*SIRT1)* (0.073), signal transducer and activator of transcription 3 (*STAT3)* (0.073), and interleukin 6 (*IL6)* (0.061). Among the miRNAs, *hsa-miR-146a, hsa-miR-34a, hsa-miR-27a, hsa-miR-155, hsa-miR-29b,* and *hsa-miR-21* showed prominent centrality values (0.061 each), reflecting their broad regulatory potential.
- Betweenness centrality analysis, which quantifies a node's control over information flow in the network, identified *VEGFA* (0.381), *hsa-miR-124* (0.341), Cyclin-Dependent Kinase 6 (*CDK6)* (0.338), *STAT3* (0.291), and *hsa-miR-34a* (0.240) as the top bridging nodes.

The dual prominence of *VEGFA* in both degree and betweenness rankings confirmed its role as the central hub and major regulatory bottleneck of the AMD miRNA–mRNA interaction network. Other nodes such as *BCL2, STAT3, IL6,* and *SIRT1* also exhibited strong centrality, suggesting their involvement in multiple signaling

cascades relevant to angiogenesis, inflammation, apoptosis, and oxidative stress—key mechanisms implicated in AMD pathogenesis.

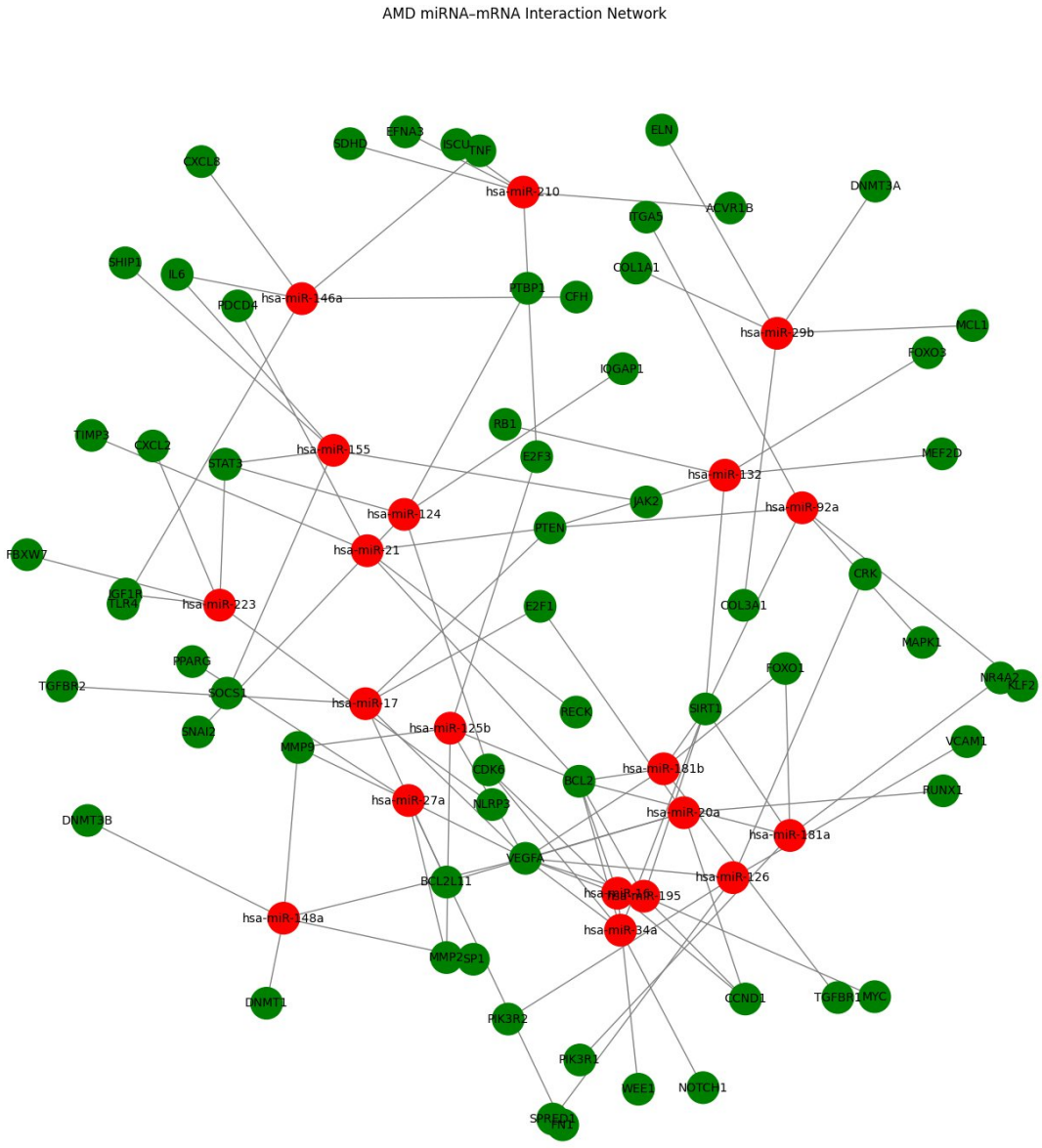

Figure 1. miRNA–mRNA interaction network in age-related macular degeneration (AMD).

Community Structure Revealed by Louvain Analysis

To uncover the modular organization of the AMD regulatory network, **Louvain community detection** was performed. The algorithm partitioned the network into **nine distinct communities**, each comprising clusters of miRNAs and mRNAs with dense intra-module connections and sparse inter-module links (Figure 2).

- **Community 1** included genes such as Reversion-Inducing Cysteine-Rich Protein with Kazal Motifs (*RECK),* phosphatase and tensin homolog *(PTEN),* mitogen-activated protein kinase 1 *(MAPK1),* Forkhead Box O3 (*FOXO3),* and retinoblastoma 1 (*RB1)*, together with *hsa-miR-21* and Tissue Inhibitor of Metalloproteinases 3 (*TIMP3)*. These genes are involved in extracellular matrix maintenance, cell survival, and regulation of angiogenesis, reflecting pathways that preserve retinal structural integrity.

Table 1. Network characteristics and top-ranked nodes by centrality measures in the AMD miRNA–mRNA network.

Class	Value
Network Characteristics	Number of nodes: 83 Number of edges: 100
Top 10 nodes by degree centrality	VEGFA: 0.122 BCL2: 0.085 SIRT1: 0.073 hsa-miR-146a: 0.061 hsa-miR-34a: 0.061 hsa-miR-27a: 0.061 hsa-miR-155: 0.061 hsa-miR-29b: 0.061 hsa-miR-148a: 0.061 hsa-miR-21: 0.061
Top 10 nodes by betweenness centrality	VEGFA: 0.381 hsa-miR-124: 0.341 CDK6: 0.338 STAT3: 0.291 hsa-miR-34a: 0.240 hsa-miR-155: 0.188 BCL2: 0.177 hsa-miR-16: 0.169 hsa-miR-125b: 0.158 SIRT1: 0.155

- **Community 2** contained *VEGFA,* runt-related transcription factor 1 *(RUNX1),* Cyclin D1 (*CCND1),* E2F Transcription Factor 1 (*E2F1),* Transforming Growth Factor Beta Receptor 2 *(TGFBR2),* and miRNAs such as *hsa-mi*R-*17, hsa-mi*R-*16,* and *hsa-mi*R-*20a.* This group represented a canonical angiogenesis and proliferation module, emphasizing the centrality of VEGF-related signaling in AMD.
- **Community 3** comprised *CDK6, SIRT1, FOXO1,* Notch Receptor 1 (*NOTCH1),* and phosphoinositide-3-kinase receptor 1 *(PIK3R1),* together with *hsa-mi*R-*34a, hsa-mi*R-*181a,* and *hsa-mi*R-*181b.* These genes and miRNAs collectively regulate cell-cycle control, oxidative stress, and metabolic adaptation, pointing to mitochondrial and senescence-related dysregulation in the retinal pigment epithelium (RPE).
- **Community 4** included *MMP2, FN1,* peroxisome proliferator-activated receptor gamma *(PPARG),* Specificity Protein 1 (*SP1),* and DNA Methyltransferase 3 Beta (*DNMT3B),* associated with *hsa-mi*R-*148a, hsa-mi*R-*125b,* and *hsa-mi*R-*27a.* This module represented epigenetic regulation and extracellular matrix remodeling, key processes in Bruch's membrane alteration and drusen formation.
- **Community 5** encompassed *IL6,* Tumor Necrosis Factor (*TNF),* Suppressor of Cytokine Signaling 1 (*SOCS1),* Janus kinase 2 *(JAK2),* Complement Factor H (*CFH),* and Toll-Like Receptor 4 (*TLR4),* with strong regulation by *hsa-mi*R-*155* and *hsa-mi*R-*146a.* Functionally, this was identified as the inflammatory and immune signaling module, integrating cytokine activity, complement activation, and innate immune regulation.
- **Community 6** consisted of *STAT3,* NOD-like receptor family pyrin domain containing 3 *(NLRP3),* Snail Family Transcriptional Repressor 2 (*SNAI2),* Insulin-Like Growth Factor 1 Receptor (*IGF1R),* and F-Box and WD Repeat Domain–Containing 7 (*FBXW7),* regulated primarily by *hsa-mi*R-*124* and *hsa-mi*R-*223.* This module likely represents signal transduction and inflammasome activation, linking transcriptional control to retinal inflammation.
- **Community 7** contained Elastin (*ELN),* Myeloid Cell Leukemia 1 (*MCL1),* Collagen Type I Alpha 1 Chain (*COL1A1),* Collagen Type III Alpha 1 Chain (*COL3A1),* and DNA Methyltransferase 3 Alpha (*DNMT3A),*

clustered with *hsa-miR-29b*. These elements were associated with collagen organization and anti-apoptotic regulation.

- **Community 8** included Phosphoinositide-3-Kinase Regulatory Subunit 2 (*PIK3R2),* Sprouty-Related EVH1 Domain–Containing Protein 1 (*SPRED1),* CRK Proto-Oncogene, Adaptor Protein (*CRK),* and Vascular Cell Adhesion Molecule 1 (*VCAM1),* connected through *hsa-miR-126,* emphasizing PI3K-Akt signaling and vascular integrity.
- **Community 9**, composed of Ephrin A3 (*EFNA3),* Iron-Sulfur Cluster Assembly Enzyme (*ISCU),* Succinate Dehydrogenase Complex Subunit D (*SDHD),* and Activin A Receptor Type 1B (*ACVR1B),* along with *hsa-miR-210,* represented hypoxia and mitochondrial metabolism-related genes, consistent with the hypoxic microenvironment of the macula.

These nine modular clusters together captured the functional heterogeneity of AMD, revealing how distinct but interconnected molecular programs—angiogenesis, inflammation, apoptosis, oxidative stress, and extracellular matrix turnover—interact through shared miRNA regulation.

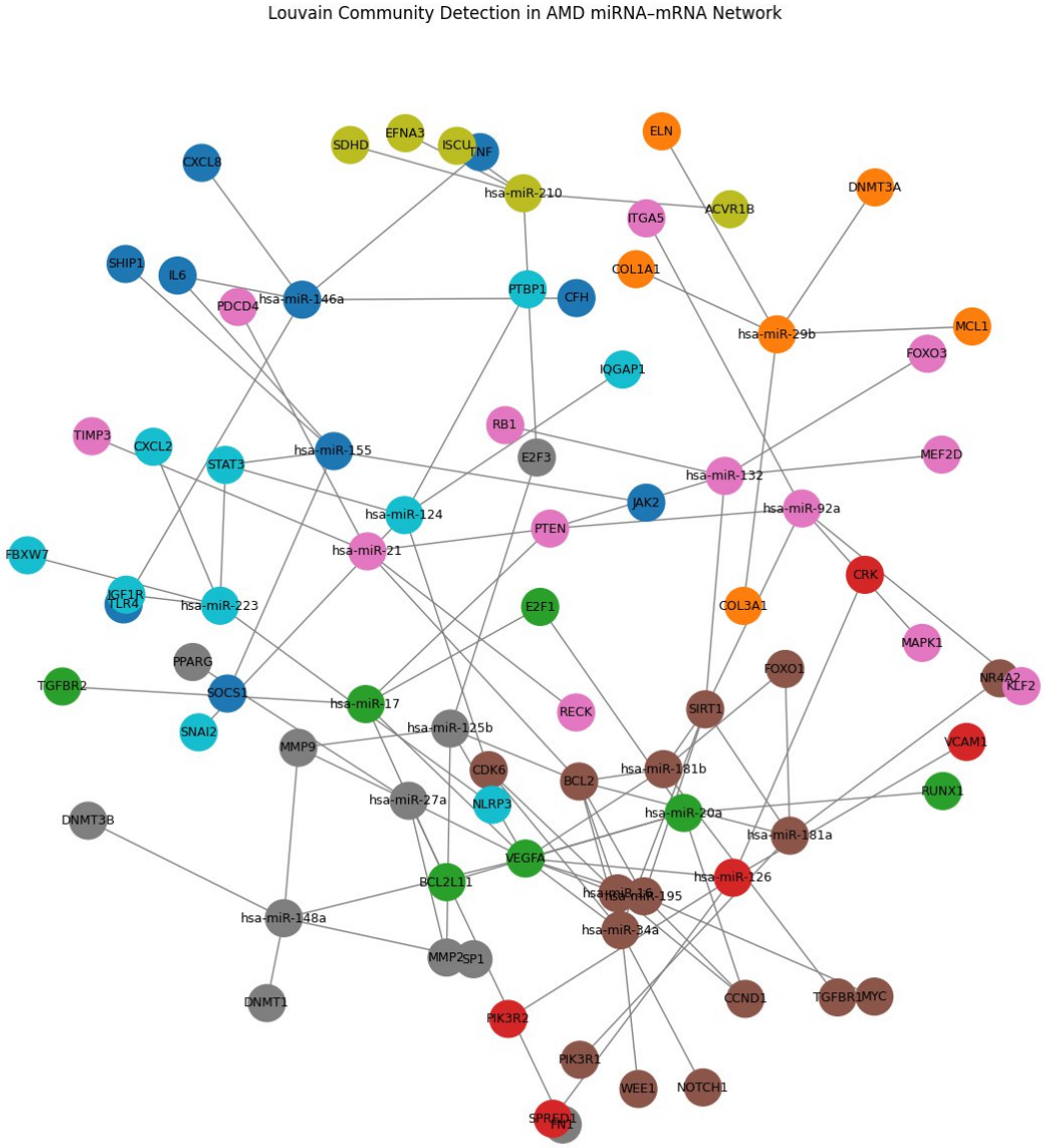

Figure 2. Community structure of the AMD miRNA–mRNA regulatory network identified by the Louvain algorithm.

Nine distinct functional modules were detected, each representing a cohesive cluster of miRNAs and their target genes. Nodes within the same color belong to the same community. The modular organization highlights the biological heterogeneity of AMD, encompassing processes such as angiogenesis, inflammation, oxidative stress, and extracellular matrix remodeling.

Functional Enrichment Analysis

Gene Ontology (GO) Enrichment

Functional enrichment of all target genes demonstrated that AMD-associated miRNA targets are significantly involved in biological processes central to retinal degeneration and stress adaptation (Figure 3). The top enriched GO Biological Process terms included:

- *Cellular response to cytokine stimulus*
- *Cytokine-mediated signaling pathway*
- *Negative regulation of cell differentiation*

These processes underscore the complex interplay between **inflammatory activation**, **cell survival**, and **oxidative stress adaptation** that underlies retinal degeneration in AMD. Many of these GO categories overlap across different Louvain communities, suggesting that multiple miRNA clusters converge on common stress-response and angiogenic mechanisms.

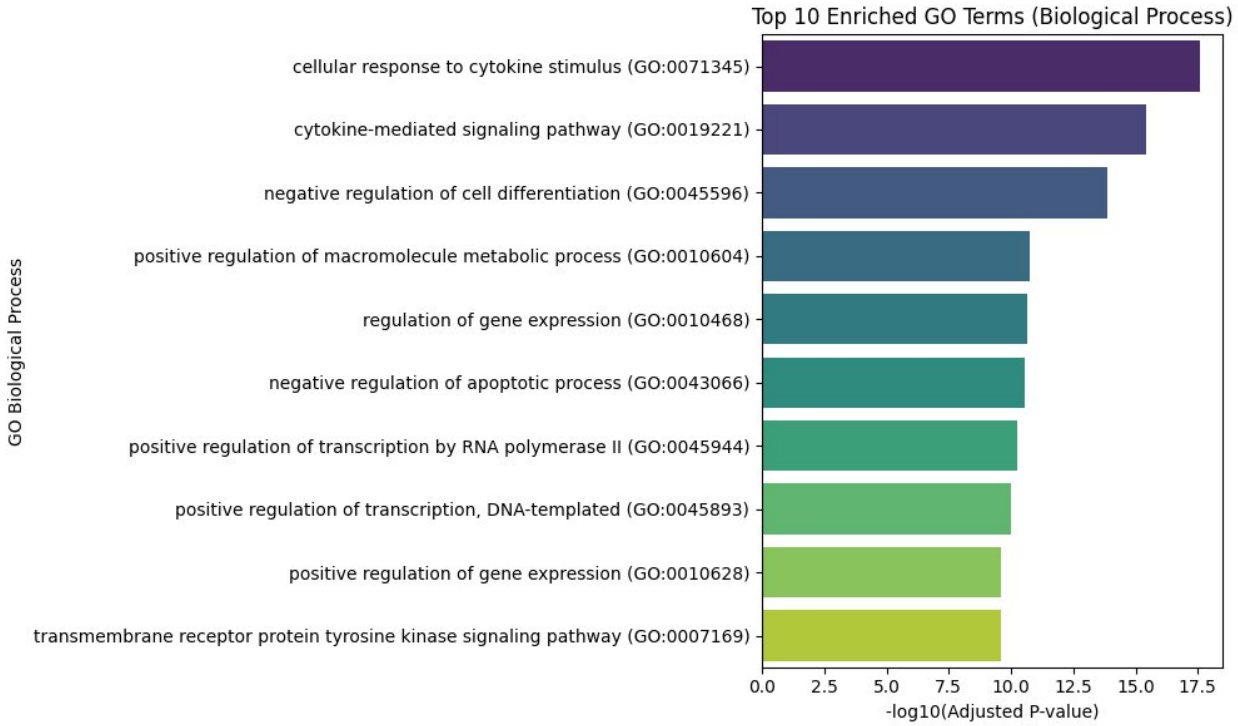

Figure 3. Gene Ontology (GO) biological process enrichment analysis of AMD-associated target genes.

Bar plot illustrating the top significantly enriched GO terms (adjusted $p < 0.05$). The length of each bar indicates the number of genes involved in the corresponding process. The most enriched terms include "cellular response to cytokine stimulus," "cytokine-mediated signaling pathway," and "negative regulation of cell differentiation," reflecting the inflammatory and stress-response nature of AMD pathology.

KEGG Pathway Enrichment

KEGG pathway analysis highlighted several highly significant signaling cascades associated with AMD pathogenesis (Figure 4). The top enriched pathways included:

- *MicroRNAs in cancer*

- *AGE-RAGE signaling pathway in diabetic complications*
- *Pathways in cancer*
- *Cellular senescence*
- *PI3K-Akt signaling pathway*

Overall, the enrichment profiles provide biological validation for the network-derived modules and confirm that the identified genes participate in interconnected mechanisms driving both the atrophic and neovascular forms of AMD.

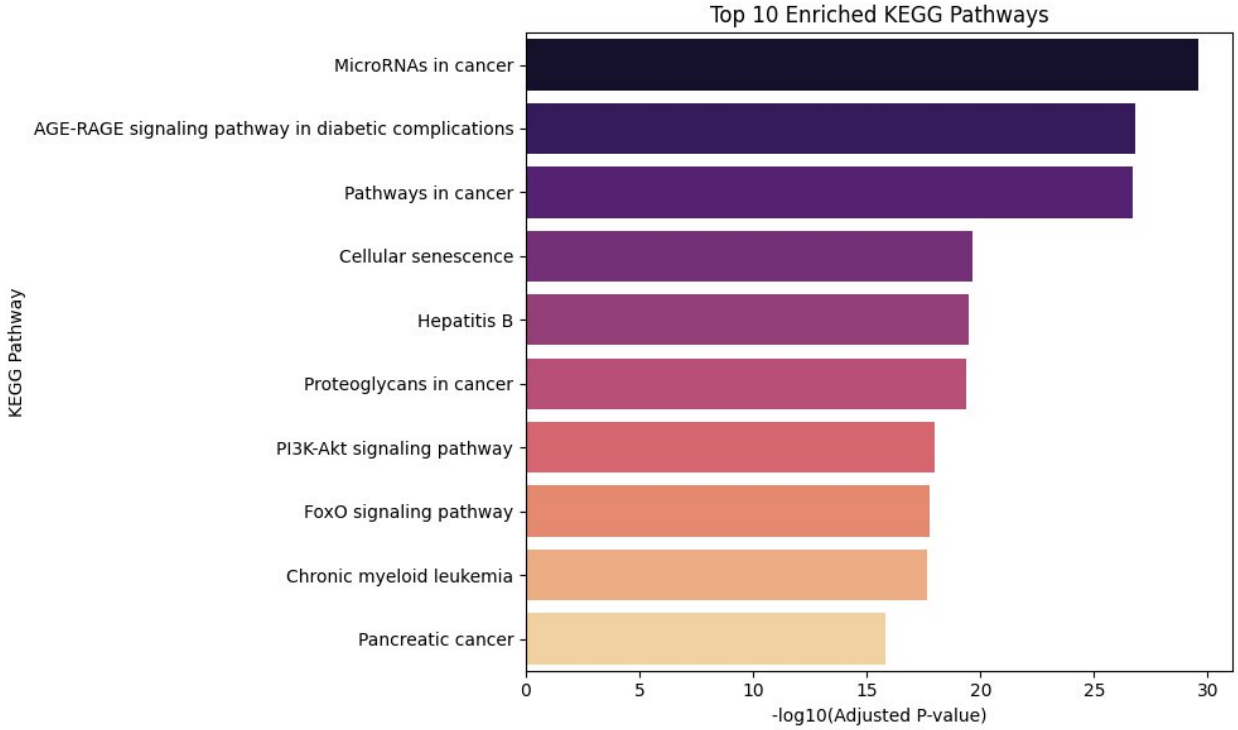

Figure 4. KEGG pathway enrichment analysis of AMD-associated target genes.

The top enriched pathways (adjusted $p < 0.05$) are shown. Prominent pathways include PI3K–Akt signaling, AGE–RAGE signaling in diabetic complications, NF-κB signaling, and cellular senescence. These pathways collectively illustrate the convergence of inflammation, angiogenesis, oxidative stress, and aging mechanisms in AMD pathogenesis.

Integrated Interpretation of Network Topology and Function

Integration of topological metrics with enrichment results revealed that hub nodes (*VEGFA, STAT3, IL6, BCL2,* and *SIRT1*) map onto the most significantly enriched biological pathways, demonstrating that central nodes are not merely topological artifacts but represent biologically pivotal regulators. The Louvain community structure corresponded closely with the functional clusters obtained from enrichment analysis, validating the **biological coherence of modular organization** within the AMD regulatory landscape.

This modular structure suggests that AMD progression involves a network of **coordinated regulatory circuits** rather than isolated signaling cascades. The findings collectively point to **miRNAs as master regulators** that orchestrate multi-gene networks involved in angiogenesis, inflammation, oxidative damage, and extracellular matrix homeostasis, thereby providing new insights into molecular cross-talk in AMD.

Discussion

VEGFA demonstrated the highest degree and betweenness centrality, confirming its pivotal position as the central hub and main bridging node in the network. Phosphoinositide-3-kinase (**PI3K)-Akt** and **cellular**

senescence pathways are particularly relevant to retinal pigment epithelial cell dysfunction [14]. Furthermore, advanced glycation end-product- receptor for advanced glycation end-products (**AGE-RAGE)** signaling underscores the contribution of chronic oxidative and glycation stress to disease progression [15]. Enrichment of nuclear factor kappa-light-chain-enhancer of activated B cells (**NF-κB)**, transforming growth factor beta (**TGF-β)**, and **complement-related** processes further supports the critical roles of inflammation and immune dysregulation in AMD.

This is consistent with the established role of vascular endothelial growth factor (VEGF) as the primary driver of choroidal neovascularization in wet AMD. Its regulation by multiple miRNAs, including *hsa-miR-16, hsa-miR-17,* and *hsa-miR-20a,* highlights a robust multi-layered mechanism controlling angiogenic signaling [16]. The redundancy in its regulatory control may reflect an evolutionary adaptation to fine-tune angiogenesis under variable environmental and metabolic stresses [17].

Other highly connected nodes—*BCL2, STAT3, IL6,* and *SIRT1*—represented key mediators of cell survival, inflammation, and oxidative stress resistance. *BCL2* and *SIRT1* function as anti-apoptotic and anti-senescence factors, whereas *IL6* and *STAT3* are central in cytokine-mediated inflammation and signal transduction [18]. The co-existence of these genes within the topological core underscores the convergence of angiogenic, inflammatory, and oxidative stress pathways in AMD. Importantly, the strong centrality of several miRNAs (e.g., *miR-146a, miR-155, miR-34a, miR-27a*) reflects their system-level influence, acting as master regulators that coordinate gene expression across multiple biological domains [19].

Community detection using the Louvain algorithm identified **nine distinct communities** within the network, revealing modular substructures with specialized biological functions. Each module contained a mixture of miRNAs and their targets, reflecting cohesive regulatory circuits.

The detection of these nine distinct but interconnected modules supports the **multifactorial model of AMD**, in which angiogenesis, inflammation, oxidative stress, and ECM dysregulation operate as interdependent processes.

The global functional enrichment analysis validated the modular observations. GO analysis revealed enrichment in processes such as *cellular response to cytokine stimulus*, *cytokine-mediated signaling*, *negative regulation of differentiation*, and *response to oxidative stress*. These terms reflect chronic inflammatory stress, impaired tissue regeneration, and metabolic reprogramming—all key components of AMD pathology [20].

KEGG pathway enrichment further revealed that target genes were significantly overrepresented in *PI3K-Akt signaling*, *AGE-RAGE signaling in diabetic complications*, *NF-κB signaling*, *cellular senescence*, and *VEGF signaling*. The PI3K-Akt pathway contributes to cell survival and angiogenesis [21,22], while AGE-RAGE signaling mediates oxidative damage and inflammation in aging tissues [23]. The enrichment of cellular senescence and NF-κB pathways reinforces the role of chronic low-grade inflammation ("inflammaging") in retinal degeneration [24]. These enriched pathways collectively demonstrate how miRNA-mediated regulation orchestrates the convergence of aging, inflammation, and angiogenesis in AMD.

The results of this study align with and extend prior findings in the literature. Several studies have identified specific miRNAs such as *miR-146a, miR-155, miR-34a,* and *miR-27a* as dysregulated in AMD patient samples or experimental models. *miR-146a* and *miR-155* have been reported to modulate the innate immune and complement pathways [25], while *miR-34a* and *miR-27a* regulate oxidative stress and angiogenesis [26]. Our network-based analysis not only confirmed these roles but also demonstrated how these miRNAs function as part of larger interconnected modules rather than isolated regulators.

Similarly, the prominence of *VEGFA, STAT3, IL6,* and *SIRT1* within the network echoes previous transcriptomic and proteomic findings implicating these genes in AMD progression [9]. However, by integrating these components into a unified regulatory network, this study provides a system-level context illustrating how individual signaling molecules interact through shared miRNA regulation.

The clinical implications of these findings are multifaceted. First, the identification of hub miRNAs and mRNAs offers potential biomarker candidates for AMD diagnosis and progression monitoring. Circulating miRNAs such as *miR-146a, miR-155,* and *miR-21* have been detected in plasma or serum of AMD patients and could reflect specific pathway activation states corresponding to distinct Louvain modules. Second, the results underscore the therapeutic potential of miRNA-based interventions. Antagomirs, chemically engineered antisense oligonucleotides designed to specifically bind and inhibit endogenous microRNAs, targeting pro-angiogenic miRNAs (e.g., *miR-20a, miR-17*) or mimics of protective miRNAs (e.g., *miR-126, miR-29b*) could complement

current anti-VEGF therapies [27]. Unlike monoclonal antibodies that inhibit a single target, miRNA-based therapy could exert a broader regulatory influence across multiple genes and pathways simultaneously. Third, module-specific insights suggest that targeting upstream regulators may achieve multifactorial modulation. For example, miRNAs in the inflammatory module (e.g., *miR-155, miR-146a*) could modulate complement activation, cytokine signaling, and macrophage polarization concurrently. Likewise, targeting the oxidative stress module (e.g., *miR-34a, miR-181 family*) may protect RPE cells from apoptosis and senescence.

This study presents a systems-level miRNA–mRNA regulatory network for age-related macular degeneration based on experimentally validated interactions. Using integrated network topology, community detection, and enrichment analyses, we identify key regulatory hubs and functional modules underlying angiogenesis, inflammation, and oxidative stress. This approach moves beyond single-miRNA analyses and provides new insight into the molecular organization of AMD. A key strength of this study is its integration of validated literature-based interactions with advanced network and enrichment analyses, providing a comprehensive systems-level overview of miRNA–mRNA regulation in AMD. The combination of centrality metrics and Louvain modularity ensured both global and local insights into network organization.

However, certain limitations warrant consideration. The curated dataset integrates interactions from diverse experimental contexts, potentially introducing bias related to tissue type or disease model. The network represents a static snapshot and does not account for temporal or spatial variations in gene expression during AMD progression. Additionally, while enrichment analyses infer functional relevance, experimental validation of predicted regulatory relationships remains essential.

Future work should incorporate high-throughput transcriptomic and small-RNA sequencing data from AMD patient tissues to refine the network and validate predicted modules. Integration with proteomic and metabolomic datasets could further elucidate cross-level interactions. Moreover, module-specific enrichment analyses and single-cell transcriptomics could identify cell-type-specific miRNA regulatory patterns within the retina and choroid.

Conclusion

This study provides a detailed systems-level map of miRNA–mRNA interactions in AMD, highlighting *VEGFA, STAT3, IL6, SIRT1,* and *BCL2* as major regulatory hubs and identifying nine distinct functional communities linked to angiogenesis, inflammation, oxidative stress, and ECM remodeling. The convergence of these pathways highlights the intricate interplay between vascular, inflammatory, and metabolic processes in the pathogenesis of AMD. From both biological and clinical perspectives, the findings emphasize that miRNAs play a key role as orchestrators of the disease network, offering novel avenues for biomarker discovery and multi-targeted therapeutic interventions.

List of Abbreviations: AMD: Age-related macular degeneration; **miRNA:** microRNA; **mRNA:** messenger RNA; **VEGFA:** vascular endothelial growth factor A; **BCL2:** B-cell lymphoma 2; **SIRT1:** sirtuin 1; **IL6:** interleukin 6; **STAT3:** signal transducer and activator of transcription 3; **GO:** Gene Ontology; **KEGG:** Kyoto Encyclopedia of Genes and Genomes; **RPE:** retinal pigment epithelium; **NF-κB:** nuclear factor kappa-light-chain-enhancer of activated B cells; **TGF-β:** transforming growth factor beta; **PI3K:** phosphoinositide 3-kinase; **Akt:** protein kinase B; **CFH:** complement factor H; **JAK2:** Janus kinase 2; **TNF:** tumor necrosis factor; **MMP2:** matrix metalloproteinase-2; **ECM:** extracellular matrix; **AGE:** advanced glycation end-product; **RAGE:** receptor for advanced glycation end-products; **NLRP3:** NOD-like receptor family pyrin domain containing 3; **PPARG:** peroxisome proliferator-activated receptor gamma; **DNMT3A/B:** DNA methyltransferase 3A/B; **CDK6:** cyclin-dependent kinase 6; **FOXO1/3:** forkhead box O1/3; **PTEN:** phosphatase and tensin homolog; **RB1:** retinoblastoma 1; **MAPK1:** mitogen-activated protein kinase 1; **IGF1R:** insulin-like growth factor 1 receptor; **VCAM1:** vascular cell adhesion molecule 1; **PIK3R1/2:** phosphoinositide-3-kinase regulatory subunit 1/2; **TIMP3:** tissue inhibitor of metalloproteinase 3; **RUNX1:** runt-related transcription factor 1; **CCND1:** cyclin D1; **Nrf2:** nuclear factor erythroid 2–related factor 2; **RECK:** Reversion-Inducing Cysteine-Rich Protein with Kazal Motifs

Author contributions: The author was involved in the study design, searching process, literature review, manuscript drafting, and revision.

Funding: This research received no funding.

Ethics Statement: The author is accountable for all aspects of the work and ensures that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement: All codes are available at: https://github.com/MehrdadMotamed-lab/AMD_miRNA/blob/main/AMD_miRNA.ipynb.

Conflicts of Interest: The author has no conflicts of interest to declare.

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